PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BB1533PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/29834	International filing date *(day/month/year)* 23 September 2003 (23.09.2003)	Priority date *(day/month/year)* 23 September 2002 (23.09.2002)

International Patent Classification (IPC) or national classification and IPC

IPC(7): C07K 1/00, 14/00, 17/00; CO7H 21/02, 21/04; C12Q 1/00; G01N 33/53; C12N 15/00,15/09,15/63,15/70 and US Cl.: 536/23.1; 530/350; 435/4, 7.1, 320.1

Applicant

E.I. DU PONT DE NEMOURS AND COMPANY

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16 April 2004 (16.04.2004)	12 October 2004 (12.10.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Brian Whiteman Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PR[redacted]NARY EXAMINATION REPORT

International [redacted]lication No.
PCT/US03/[redacted]

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-53 as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the claims:
pages 54-58 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the drawings:
pages 1-38 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-589 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PR[redacted]INARY EXAMINATION REPORT

International [redacted]lication No.
PCT/US03/[redacted]

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 17 and 21-33

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. ____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 17 and 21-33

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PR[redacted]INARY EXAMINATION REPORT

Internation[redacted]plication No.
PCT/US0[redacted]4

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-16 and 18-20	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-16 and 18-20	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-16 and 18-20	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-16 and 18-20 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an isolated nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO: 2.

Claims 1-16 and 18-20 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry for producing a ryanodine receptor using an in vitro cell comprising an isolated nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO: 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/29834

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07K 1/00, 14/00, 17/00; C07H 21/02, 21/04; C12Q 1/00; G01N 33/53; C12N 15/00,15/09,15/63,15/70
US CL : 536/23.1; 530/350; 435/4, 7.1, 320.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/23.1; 530/350; 435/7.1, 320.1, 455

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/71042 A2 (PE CORPORATION) 27 September 2001 (27.09.2001), see whole document, especially pages 1-7.	1-15
A	TAKESHIMA et al. Isolation and characterization of a gene for a ryanodine receptor/calcium release channel in drosophila melangoaster. FEBS Letters. 1994, Vol. 337, pages 81-87.	1-9, 11-15
A	US 2001/0046664 A1 (MURPHY et al.) 29 November 2001 (29.11.01), see whole document, especially pages 11 and 13-14.	1-9,11-16,19,20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2004 (23.07.2004)	20 SEP 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Brian Whiteman Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/29834

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-16, 18, 19, 20 (SEQ ID NOs: 1 and 2)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/29834

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-16, 18, 19, 20, drawn to an isolated nucleotide sequence encoding an amino acid sequence identity of at least 80% when compared to a polypeptide consisting of SEQ ID NO: 2, an isolated nucleic acid sequence of SEQ ID NO: 1, construct and transformed host cell comprising said nucleotide sequence and a method of evaluating at least compound for its ability to modulate homeostasis using said host cell.

Group II, claim(s) 1-16, 18, 19, 20, drawn to an isolated nucleotide sequence encoding an amino acid sequence identity of at least 80% when compared to a polypeptide consisting of SEQ ID NO: 4, an isolated nucleic acid sequence of SEQ ID NO: 3, construct and transformed host cell comprising said nucleotide sequence and a method of evaluating at least compound for its ability to modulate homeostasis using said host cell.

Group III, claim(s) 1-16, 18, 19, 20, drawn to an isolated nucleotide sequence encoding an amino acid sequence identity of at least 80% when compared to a polypeptide consisting of SEQ ID NO: 8, an isolated nucleic acid sequence of SEQ ID NO: 7, construct and transformed host cell comprising said nucleotide sequence and a method of evaluating at least compound for its ability to modulate homeostasis using said host cell.

Group IV, claim(s) 1-16, 18, 19, 20, drawn to an isolated nucleotide sequence encoding an amino acid sequence identity of at least 80% when compared to a polypeptide consisting of SEQ ID NO: 10, an isolated nucleic acid sequence of SEQ ID NO: 9, construct and transformed host cell comprising said nucleotide sequence and a method of evaluating at least compound for its ability to modulate homeostasis using said host cell.

Group V, claim(s) 17 and 18, drawn to a method for evaluating at least one compound which modulates a ryanodine receptor activity, the method comprising contacting at least one compound with a polypeptide encoded by the nucleic acid sequence set forth in SEQ ID NO: 2.

Group VI, claim(s) 17 and 18, drawn to a method for evaluating at least one compound which modulates a ryanodine receptor activity, the method comprising contacting at least one compound with a polypeptide encoded by the nucleic acid sequence set forth in SEQ ID NO: 4.

Group VII, claim(s) 17 and 18, drawn to a method for evaluating at least one compound which modulates a ryanodine receptor activity, the method comprising contacting at least one compound with a polypeptide encoded by the nucleic acid sequence set forth in SEQ ID NO: 8.

Group VIII, claim(s) 17 and 18, drawn to a method for evaluating at least one compound which modulates a ryanodine receptor activity, the method comprising contacting at least one compound with a polypeptide encoded by the nucleic acid sequence set forth in SEQ ID NO: 10.

Group IX, claim 21, drawn to an isolated nucleic acid fragment encoding a combination of polypeptides set forth in SEQ ID NO: 63-119. The first combination is SEQ ID NO: 63 and 64. The number of possible combinations is 56! "functional".
If applicants want additional combination(s) to be searched, applicants are required to define the combination and pay an additional search fee for each single combination of 2 or more polypeptides because each combination is considered drawn to a single invention. Each additional combination is an additional search fee of $210.

Group X, claims 22 and 23, drawn to a method for identifying a nucleic acid sequence encoding an insect ion channel comprising obtaining an isolated nucleic acid encoding a first polypeptide having at least 100 amino acids and comparing a polypeptide selected from the group consisting of SEQ ID NOs: 63-119. The first combination is SEQ ID NO: 63 and 64. The number of possible combinations is 56! "functional".
If applicants want additional combination(s) to be searched, applicants are required to define the combination and pay an additional search fee for each single combination of 2 or more polypeptides because each combination is considered drawn to a single invention. Each additional combination is an additional search fee of $210.

Group XI, claim(s) 24, 27, 28, 29, 32, and 33, drawn to a method for expressing an isolated nucleic acid fragment encoding a toxic insect ion channel which comprises transforming a host with a recombinant construct comprising in the 5' to 3' direction a promoter operably linked to the toxic insect ion channel nucleic acid wherein the promoter comprises a transcription termination nucleic acid fragment situated between said promoter and the isolated nucleic acid fragment encoding the toxic insect ion channel.

Group XII, claim(s) 25, 27, 28, 30, 32, and 33, drawn to a method for expressing an isolated nucleic acid fragment encoding a toxic insect ion channel which comprises transforming a host with a recombinant construct comprising in the 5' to 3' direction a promoter operably linked to the toxic insect ion channel nucleic acid wherein the promoter comprises a nucleic acid fragment comprising at least one in-frame translational termination codon situated between said promoter and the isolated nucleic acid fragment encoding the toxic insect ion channel.

Group XIII, claim(s) 26, 27, 28, 31, 32, and 33 drawn to a method for expressing an isolated nucleic acid fragment encoding a toxic insect ion channel which comprises transforming a host with a recombinant construct comprising in the 5' to 3' direction a promoter operably linked to the toxic insect ion channel nucleic acid wherein the promoter comprises a nucleic acid fragment consisting essentially of at least one transcription termination nucleic acid fragment and at least one in-frame translational termination codon situated between said promoter and the isolated nucleic acid fragment encoding the toxic insect ion channel.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

a) SEQ ID NO: 128, 130, 144, and 146 in claim 1.

b) SEQ ID NO: 127, 129, 143, and 145 in claim 6.

The claims are deemed to correspond to the species listed above in the following manner:

Claims 1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14, 15, 16, 19, and 20 correspond to the species of a).

The following claim(s) are generic: claims 1 and 11.

Claim 6 corresponds to the species of b).

The following claim(s) are generic: Claim 6.

The inventions listed as Groups I-XIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of Group I is considered to be drawn to SEQ ID NO: 2.

The special technical feature of Group II is considered to be drawn to SEQ ID NO: 4.

The special technical feature of Group III is considered to be drawn to SEQ ID NO: 8.

The special technical feature of Group IV is considered to be drawn to SEQ ID NO: 10.

The special technical feature of Group V is considered to be drawn to a method for evaluating at least one compound which modulates a polypeptide consisting of at least 80% when compared to SEQ ID NO: 2.

The special technical feature of Group VI is considered to be drawn to a method for evaluating at least one compound which modulates a polypeptide consisting of at least 80% when compared to SEQ ID NO: 4.

The special technical feature of Group VII is considered to be a method for evaluating at least one compound which modulates a polypeptide consisting of at least 80% when compared to SEQ ID NO: 8.

The special technical feature of Group VIII is considered to be a method for evaluating at least one compound which modulates a polypeptide consisting of at least 80% when compared to SEQ ID NO: 10.

The special technical feature of Group IX is considered to be an isolated nucleic acid fragment encoding an insect ion channel comprising at least two polypeptide sequences set forth in any of SEQ ID NOs: 63-119. The common structural feature for SEQ ID NOs: 63-119 is

not disclosed in the disclosure. Therefore, the technical feature linking the combination of two or more polypeptides lack the same or corresponding technical feature.

The special technical feature of Group X is considered to be a method of identifying a nucleic acid sequence encoding an insect ion channel comprising comparing a polypeptide to a polypeptide selected from the group consisting of SEQ ID NOs: 63-119. The common structural feature for SEQ ID NOs: 63-119 is not disclosed in the disclosure. Therefore, the technical feature linking the combination of two or more polypeptides lack the same or corresponding technical feature.

The special technical feature of Group XI is considered to be a method of using a construct comprising a promoter comprising a transcription termination nucleic acid fragment.

The special technical feature of Group XII is considered to be a method of using a construct comprising a promoter comprising at least one in-frame translational termination codon.

The special technical feature of Group XIII is considered to be a method of using a construct comprising a promoter comprising a transcription termination nucleic acid fragment and at least one in-frame translational termination codon.

Accordingly, Groups I-XIII are not so linked by the same or a corresponding special technical feature as to form a single inventive concept

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: the species of (a) the amino acid sequences are different structurally and the disclosure does not disclose a common structural feature for the amino acid sequences; (b) the nucleotide sequences are different structurally and the disclosure does not disclose a common structural feature for the nucleotide sequences.

Continuation of B. FIELDS SEARCHED Item 3:
WEST2.1, STN
search terms: ryanodine receptor, construct, calcium homeostasis, cell, oligomer, ion channel